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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,450	09/05/2003	F. Charles Brunicardi	60710-00002USC1	8472

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

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07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,450	BRUNICARDI, F. CHARLES	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-153* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-153* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/16/07 has been entered.

Applicant's arguments filed 5/16/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 119-153 are pending and under consideration. Claims 1-118 are canceled.

Terminal Disclaimer

The terminal disclaimer filed on 5/16/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of patent No, 6,716,824 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-153 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing a pancreatic tumor cell that

does not express insulin in a subject by directly administering to a subject a nucleic acid comprising a vector with an insulin promoter having SEQ ID NO: 1 operably linked to a cytotoxic gene, wherein the cytotoxic gene is thereby expressed in the pancreatic tumor cell that is PDX-1 positive and administering a prodrug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing said cell, does not reasonably provide enablement for treating a pancreatic tumor in a subject by systemic administration of the of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 119-153 are directed to a method of killing a pancreatic tumor cell that does not express insulin in a subject, by administering to a the subject a nucleic acid comprising a vector with an insulin promoter having SEQ ID NO:I operatively coupled to a cytotoxic gene, wherein the administration of the nucleic acid is either by direct administration at the site of the, pancreatic tumor cell that does not express insulin or by systemic administration via liposomal or adenoviral delivery and wherein the cytotoxic gene is thereby expressed in a the pancreatic tumor cell that does not express insulin, and b) administering a prodrug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the pancreatic tumor cell that does not express insulin.

The specification describes that the present invention is directed to selective targeting of pancreatic cells with cytotoxic genes for treating cancer and other diseases (specification p 7). The specification teaches a decrease in the tumor burden of SCID mice injected intraperitoneally (IP) with PANC-1 human adenocarcinoma pancreatic cancer cells followed by IP injection of liposomes complexes with rat insulin promoter

(SEQ ID NO: 1)-thymidine kinase (RIP-TK) nucleic acid followed by GCV [168]. However the specification fails to provide any relevant teachings or specific guidance and/or working examples with regard to killing any pancreatic tumor cell in vivo by systemic administration of said nucleic acid. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for killing a pancreatic tumor cell by systemic administration of said nucleic acid. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

At the time of the instant invention the art of suicide gene therapy was unpredictable with regard to systemic administration of said nucleic acid without undue experimentation. With regard to selectively killing of any pancreatic tumor cell by using systemic delivery of RIP-tk/GCV gene therapy as contemplated by the instant specification [69], the state of the art of a cytotoxic gene and a prodrug mediated gene therapy (suicide gene therapy) suggests that while some progress has been made to date there are issues that remain, which make sucidal gene therapy treatment unpredictable. **Nasu et al,** (Mol Urol, 4(2): 67-71, 2000) noted that viral-mediated transfer of the herpes simplex virus thymidine kinase (HSV-tk) is still in the early stage of its development, with a number of problems to be overcome **such as systemic delivery**, specific introduction, and specific expression of the target gene are the major issues to be managed in order to establish a relevant treatment (abstract). **Hunt et al,** (Science, 297: 415-416, 2002) notes liposomes and other nonviral delivery systems at present the efficacy of these systems is limited largely by poor transduction efficiencies (p 416, 2nd column, 3rd paragraph). Moreover, Hunt reports though the opportunity for systemic delivery with predictable pharmacokinetics is attractive (p 416, 2nd column, 3rd paragraph), direct injection of vectors containing therapeutic genes may result in

regression of the tumor at the injection site but is unlikely to affect tumor cells at distant sites (p 416, 2nd column, 4th paragraph). Hunt notes a major restriction in treating cancer with gene therapy is the limitations in specifically targeting tumor cells, especially cells that have metastasized into the systemic circulation and there is a need for (i) development of vectors to treat systemic disease and prolong gene expression, (ii) specific targeting of vectors to achieve tumor-selective binding (p 415, 1st column). **MacKenzie** (Lancet Oncology, 5: 541-49,2004) wile reviewing the state of the art of gene therapy in pancreatic adenocarcinoma noted that suicide-gene therapy has produced variable results in animal studies on pancreatic cancer and while some studies showed that suicide-gene treatment decreased survival of tumor cells in vitro and in vivo however, other studies have **not** confirmed the efficacy of suicide genes in pancreatic cell lines (p 542, 2nd column under suicide gene therapy). MacKenzie also noted that although suicide gene approach has not been assessed in patients with pancreatic cancer, results from other tumor sites have **not** been encouraging (p 542, 2nd column under suicide gene therapy). **Fogar et al,** (EJSO, 29: 721-730, 2003) noted that suicide gene therapy with HSV-TK did not confer GCV sensitivity to pancreatic cancer in vivo and different pancreatic cancer cell lines cause different growth effects and metastasis patterns after inoculation into SCID mice (abstract). Three years after the filing of the instant application **Fogar et al,** (Cell Mol Biol, 51(1): 61-76, 2005) while reviewing killer genes in pancreatic cancer therapy and among them the use of suicide genes (HSV-TK and CD for pancreatic cancer gene therapy in vitro and in vivo noted that the lack of a 100% effect for any studied strategy considered alone, indicates the need for combined therapies to achieve a satisfactory treatment of pancreatic tumor (abstract).

At the time of the instant invention **Robbins et al,** (Pharmacol Ther, 80(1): 35-47, 1998) notes that a gene encoding an enzyme able to convert a prodrug to an active drug

such as HSV-TK can be delivered and for certain types of tumors a bystander-killing effect can be observed with a suicide gene such that only a percentage of the tumor cells need to be transduced for eradication of a tumor (p 43, 2nd column, 1st paragraph). Unfortunately, these approaches do not necessarily treat secondary, distal tumors that are not directly accessible by gene transfer (Robbins, p 43, 2nd column, 1st paragraph). Robbins also notes poor dissemination of retrovirus for example is responsible for the level of insufficient infection in TK-expressing retroviruses (p 43, 2nd column, 1st paragraph).

In view of the art the working examples do not provide guidance for systemic administration of RIP-TK in a subject resulting in killing or treating insulin negative or PDX-1 positive pancreatic tumor cells because the IP administration of RIP-TK does not correlate with the systemic administration of RIP-TK as set forth by the issues raised by the art as discussed above.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject by systemic administration, the lack of direction or guidance provided by the specification for the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject by systemic administration, the absence of working examples that correlate to the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject by systemic administration, the unpredictable state of the art with respect to the cytoxic gene and prodrug gene therapy, and in particular in pancreatic tumor cells, the undeveloped state of the art pertaining to the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject, and the breadth of the claims directed to pancreatic tumors cells that does not express insulin, or PDX-1 positive and also cytotoxic gene vectors comprising SEQ ID NO: 2 or SEQ ID NO: 3, it would have required undue experimentation for one skilled in

the art to make and/or use the claimed invention.

Applicants argue that have provided in vivo data demonstrating that liposomal delivery (e.g., of the RIP-TK construct) is efficacious. Applicant argue, as noted in APPENDIX 2 and the "DECLARATION UNDER 37 CFR § 1.132 OF F. CHARLES BRUNICARDI," that, in addition to direct administration of nucleic acid at the site of a tumor cell, systemic administration of nucleic acid, whether via liposomal delivery or adenoviral delivery, is enabled. Applicants argue after describing in paragraph [0068] the injection of PANC-1 cells into scid mice and the liposomal delivery of a RIP-tk gene construct (as well as a control RIP-lacZ gene construct to the mice, paragraph [0069] reports: [0069] "At necropsy, all nine mice treated with the gene therapy/GCV had no visible pancreatic tumors and one of nine had microscopic tumors on the liver. All control groups had large tumors. These data confirm that human PANC-1 cells can be selectively killed using systemic delivery of RIP-tk/GCV gene therapy"

These arguments are not persuasive because neither the specification nor the Declaration, Appendix 1 or Appendix 2 describes systemic administration of RIP-TK nucleic acid into scid mice. The positive results seen with the IP injection of RIP-TK nucleic acid into scid mice cannot be extrapolated into systemic administration of RIP-TK into scid mice. The mere statement that "At necropsy, all nine mice treated with the gene therapy/GCV had no visible pancreatic tumors and one of nine had microscopic tumors on the liver. All control groups had large tumors. These data confirm that human PANC-1 cells can be selectively killed using systemic delivery of RIP-tk/GCV gene therapy" which refers to the IP injection of the RIP-TK into scid mice cannot be extrapolated into systemic administration of RIP-TK. This is because the art teaches that the mode of administration of a suicidal gene for gene therapy is unpredictable as discussed by Robbins for example. **Nasu et al,** also noted that viral-mediated transfer of

the herpes simplex virus thymidine kinase (HSV-tk) is still in the early stage of its development, with a number of problems to be overcome **such as systemic delivery**, specific introduction, and specific expression of the target gene are the major issues to be managed in order to establish a relevant treatment. Gene transfer vector biodistribution is a pivotal issue for determination of target organs or tissues for toxicity and determination of speading of vectors in the gene transfer recipient and transgene expression. For example, results discrepancy between species or preclinical settings underscore the importance of the anatomic topography of the vein used for intravascular (systemic) biodistribution testing where results from a tail vein injection differ from those of ear or portal injection independent of the species effect (Gonin et al, (Gene Therapy, 11: S98-S108, 2004) (p S106, 1st column). Regarding intraperitoneal administration of gene transfer vector the biodistribution of a vector does not require crossing of the blood endothelium as caution must be taken about blood endothelium trapped vector by systemic administration.

It is noted Applicants in Appendix, Claims 119-153 renumbered as claims 1-35 and reordered. Applicants are advised that the numbering of claims is not accordance with 37 CFR 1.126, which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). See MPEP 608.01(j) Numbering of Claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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